EXHIBIT O

Time Trends of Non-Hodgkin's Lymphoma: Are They Real? What Do They Mean?[1]

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Abstract

Factors that need to be considered in the analysis of time trends in disease incidence are age, year of diagnosis, and birth cohort. When these are included in a log-linear model, a nonidentifiability problem arises from the linear dependence among these three time factors so that only specified functions of the parameters can be unambiguously determined. One of these invariant functions is the drift or the sum of the period and cohort trend. Non-Hodgkin's lymphoma incidence rates from Connecticut for the period 1935–1989 were analyzed for males and females. In addition to an age effect, both period and cohort significantly improved the fit of the model. The estimated drift shows that there has been a 10.3% increase in risk every 5 years since 1965 for females and 9.2% for males. It is unlikely that a trend of this magnitude can be attributed entirely to data artifact.

Introduction

The analysis of time trends for disease incidence is an important first step in understanding the etiology of a disease. While such analyses have proven uses, there are also underlying limitations to their interpretation so that some of the knowledge we seek to gain from an analysis of trends in rates will inevitably elude us. Three fundamental time effects that should be considered when investigating trends in disease rates are (*a*) age at diagnosis, (*b*) period or year of diagnosis, and (*c*) cohort or the year in which an individual was born (1).

There are many reasons for studying time trends in disease incidence, aside from the information they provide for assessing the health care needs of the population. Time trends have sometimes furnished valuable clues to disease etiology, leading to more definitive studies of the causes of disease. In addition, trends in population-based rates are the ultimate result of population changes in risk factor exposure so that understanding these interrelationships in a specified population can assist in the development of strategies for disease control.

The fact that risk for many cancers is associated with the aging process is well recognized; therefore, it almost goes without saying that age should be part of any descriptive model of cancer trends.

Period, or year of diagnosis, on the other hand, can be affected by any factor that increases the risk of a cancer diagnosis for all age groups. This might be due to exposure of all ages to an etiological agent, such as the exposure that one might expect to come from something in the air or water. However, it might also be induced by artifactual changes in the methods of diagnosis. For example, this may be the result of changes in medical technology and/or the extent to which more sensitive methods of diagnosis are used in clinical practice. In addition, one cannot ignore the possibility that there are occasionally fads in selecting a particular diagnosis. These artifactual changes do not represent real changes in the health of the public, but they are only changes in the way disease is classified.

Exposure to a causal factor at birth might be manifested as a cohort effect. However, these are really more general than factors related to birth in that they represent a generation factor; therefore, if the risk of disease varies by generation, then we might expect to see a cohort effect. Changes in risk factor exposure that only affect a particular age group induce an increased risk that becomes associated with the generation that is at the appropriate age when exposure changes. For instance, the strong cohort trends for lung cancer have been attributed to cigarette smoking, because the habit tends to be started in a fairly narrow age range, the late teens to early 20s, and it is the leading cause of the disease (2, 3). While data artifact caused by change in diagnostic patterns would seem to have the greatest influence on the period effects, we cannot rule out the possibility that cohort could be affected by data artifact as well. Some generations might be less tolerant of uncomfortable medical procedures required for a definitive diagnosis, which could, in turn, induce an artifactual cohort trend. In addition, subgroups such as the elderly may be utilizing a component of the health care system that is not using the latest diagnostic procedures so that they have a different probability of receiving a particular diagnosis.

Materials and Methods

For many years, epidemiologists have recognized some of the important etiological implications that may arise from these three time factors. However, it was not until researchers tried to model these factors in a more formal way that the fundamental inferential limitations were more fully appreciated. This arises from the linear dependence among these factors (4), in that the year of birth can be directly calculated by taking the difference between the period and the age,

$$\text{Cohort} = \text{Period} - \text{Age}$$

To understand the associations in a regression analysis, it is generally recommended that linearly dependent variables not be included in the analysis. However, the implications of this dependence are really much deeper than just the problem of fitting a regression model. It really involves any attempt to interpret time trends, including simple graphs of age-specific rates. Therefore, one really needs to grapple with, rather than ignore, this problem.

When one tries to represent the overall trend or slope for a particular time effect, then the linear dependence implies that each slope can only be determined up to an unidentifiable constant. If β is the expected value of the slope for one of the time factors that arises from a particular method of estimation, and β' is the true slope, then there is an indeterminate constant that affects all three slopes for the time factors. This can be represented as

$$\beta_a = \beta'_a + \nu$$
$$\beta_p = \beta'_p - \nu \qquad \text{(A)}$$
$$\beta_c = \beta'_c + \nu$$

where β_a is the age slope, β_p is the period, β_c is the cohort, and the indeterminate constant is represented by ν (5).

We can derive two important facts from the relationship among the slopes shown in Equation A. First, none of the slopes can be determined, and each can, in principle, take any value (6), suggested here by

adding and subtracting the arbitrary constant ν. Second, there is an interdependence among the slopes; therefore, if one of the parameters is fixed, resulting in a specification of ν, then the other two parameters are defined as well. For some cancers, it may be possible to bring outside information to bear on the estimate of ν. This information might include trends in exposure to known risk factors for the disease, as well as theoretical models for the carcinogenesis process. After we determine ν, then all three time parameters are identified. However, it is not always possible to obtain a valid estimate of ν.

The interrelationships among the slopes also imply that certain of their functions can be uniquely determined (5, 6). For example, if we add the period and cohort slopes, the constant, ν, cancels out, and we have a unique parameter. This sum, $\beta_p + \beta_c = \beta_p' + \beta_c'$, has been referred to as the drift parameter by Clayton and Schifflers (7, 8), and it can be useful as an indication of the overall trend for the rates.

In general, one does not wish to limit the model to effects that are linear, so we will use a more general representation for describing trends. The rate for age i, period j, and cohort k is given by the log-linear model

$$\log \lambda_{ijk} = \mu + \alpha_i + \pi_j + \gamma_k \qquad \text{(B)}$$

where α_i ($i = 1,...,I$) is the effect of age, π_j ($j = 1,...,J$) is the effect of period, and γ_k ($k = j - i + I$) is the effect of cohort. Because this representation has too many parameters, we apply the usual constraints on the parameters, $\Sigma_i \alpha_i = \Sigma_j \pi_j = \Sigma_k \gamma_k = 0$. To incorporate the non-identifiable component that is inherent in these models, we express each of the time effects in terms of an overall linear trend, along with a remaining curvature or departure from that trend. For example, the age effect becomes

$$\alpha_i = \beta_a \left(i - \frac{I+1}{2} \right) + \alpha_{ci} \qquad \text{(C)}$$

where β_a is the slope and α_{ci} is the departure from linear trend for the ith age group. It is important to note that the curvature components of the model are estimable, $i.e.$, they are uniquely determined (5, 6, 9). Only the slopes are not determined, and these are interrelated by a single unidentifiable constant, as described in Equation A (5).

One might be tempted to think that the implications of some of these results are avoided by statistical methods that do not use models, such as direct adjusted rates. This is not true, because these adjustments generally ignore the effect of cohort, which is only reasonable when the effect is not related to the rate.

This analysis is based on all non-Hodgkin's lymphoma cases reported to the Connecticut Tumor Registry between 1935 and 1988. Data were first tabulated, using 5-year age groups (20 through 84 years) and 5-year periods, with the exception that the last period is only 4 years. Denominators for the rates were obtained by cumulating the mid-year population estimates obtained by the Connecticut State Health Department, which provides an estimate of person-years experience.

To estimate the effect of these time factors on non-Hodgkin's lymphoma incidence, we fitted the log-linear age-period-cohort model, shown in Equation B to the Connecticut incidence data. It was assumed that the number of cases had a Poisson distribution, and maximum likelihood estimates of the parameters were obtained by using the regression package, GLIM (generalized linear interactive modeling) (10).

Results

To understand the implications of the underlying time factors for non-Hodgkin's lymphoma, we first consider the trends for the age-specific rates. Fig. 1A shows the age-specific rates plotted against period of diagnosis for females. If the only two factors affecting the age-specific rates were age and period, then these lines should be parallel on either the log or arithmetic scale. This graph shows incidence rates plotted on the log scale, but the suggested lack of parallelism in these data is just as apparent using the additive scale. A similar graph can be con-
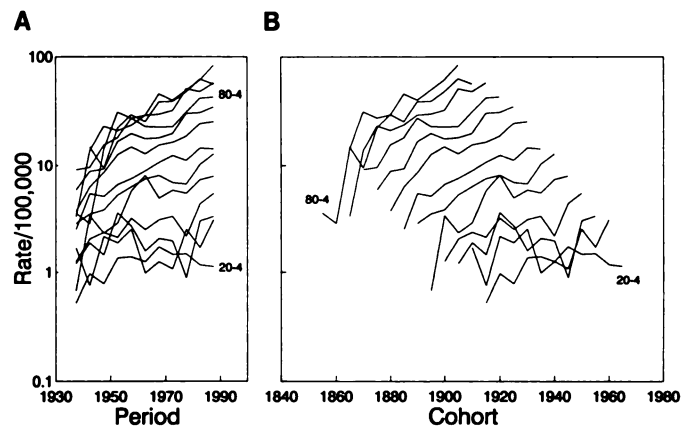

Fig. 1. Age-specific incidence rates of non-Hodgkin's lymphoma for Connecticut females from 1935–1989 by (A) period and (B) cohort.

structed to view the effect of cohort on the age-specific rates, shown in Fig. 1B. Fig. 2 shows the corresponding age-specific rates for males, plotted against period (A) and cohort (B).

For males, there were no cases in the earliest cohort, represented in these data by those 80–84 years in the 1935–1939 birth cohort and only three in the next cohort. Similarly, in females, there was only one case in each of the oldest two cohorts. Because of these small numbers, the first two cohorts were excluded from the model fitting. The significance tests derived from fitting the age-period-cohort model to these data are summarized in Table 1. The goodness of fit tests were less than the degrees of freedom for both genders, suggesting that the model gives a reasonable description of these data. In addition, both period and cohort were significant factors in describing the trends in incidence rates. Because of the nonidentifiability problem described above, the period and cohort tests are only considering curvature, because the linear components are hopelessly confounded (5, 6). A separate test for age is not shown because we believe a $priori$ that it has a strong effect on incidence; therefore, a model without it should not be seriously considered.

Fig. 3 shows several specific sets of age, period, and cohort parameters for females in Connecticut. Several parameter sets are shown to emphasize the fact that a unique set is not available because of the nonidentifiability problem alluded to earlier. The solid line is based on an assumption of no overall period trend, or zero period slope, and that assumption results in a steady upward trend for the cohort effects shown by the corresponding solid cohort line. Changes in diagnostic practice (a
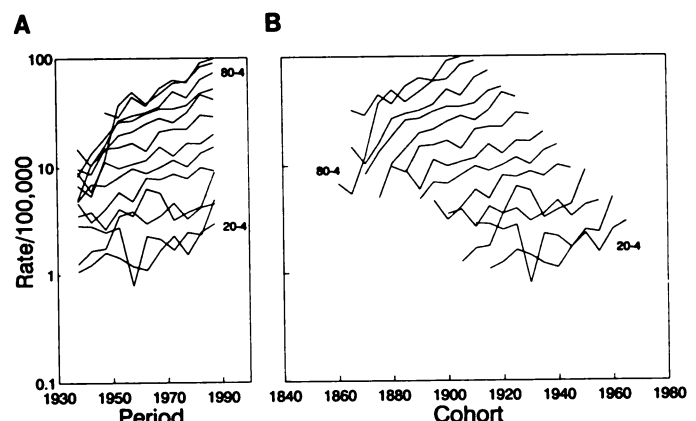

Fig. 2. Age-specific incidence rates of non-Hodgkin's lymphoma for Connecticut males from 1935–1989 by (A) period and (B) cohort.

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Table 1 *Significance tests for goodness of fit and time effects for the age-period-cohort model*

Source		Likelihood ratio test	
	d.f.	Males	Females
Goodness of fit	99	86.80	90.84
Cohort curvature	21	100.70[a]	68.19[a]
Period curvature	9	27.57[b]	35.46[a]

[a] P < 0.001.
[b] P < 0.01.
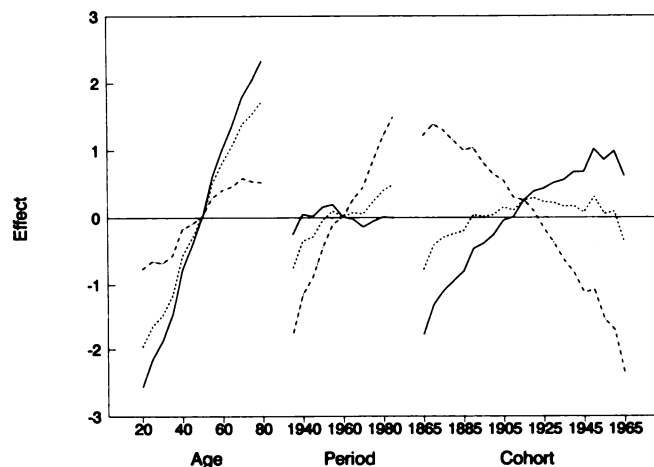
Fig. 3. Age, period, and cohort effects for females constrained so that the sum is 0 ($\beta_p = 0$ for *solid line*, $\beta_p = 0.1$ for *dashed line*, $\beta_p = 0.2$ for *dotted line*, and $\beta_p = 0.3$ for *dot-dashed line*).
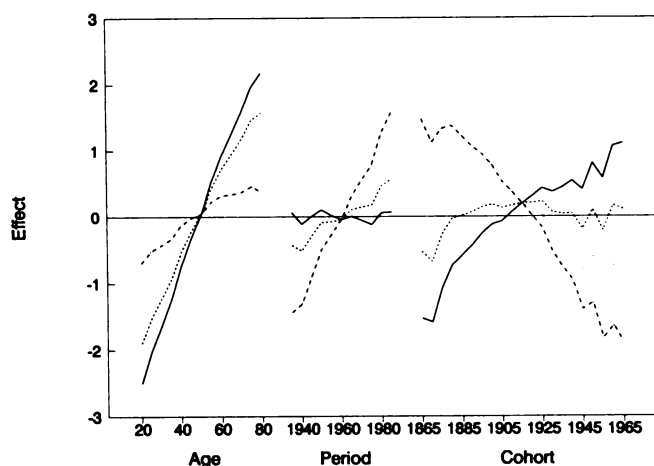
Fig. 4. Age, period, and cohort effects for males constrained so that the sum is 0 ($\beta_p = 0$ for *solid line*, $\beta_p = 0.1$ for *dashed line*, $\beta_p = 0.2$ for *dotted line*, and $\beta_p = 0.3$ for *dot-dashed line*).

period effect) suggest that one should expect some increase due to this data artifact. If the magnitude of the increase was appropriately represented by the dashed line, then the corresponding cohort effects would indicate a relative flattening of the more recent cohort trends. Even larger slopes for period result in a corresponding decline for the cohort effect, and we should not ignore the corresponding changes in the age effects, which have been eroded substantially for the steepest period trends shown by the dash-dot line. Using only the observed rates, we cannot sort out which of these models is best, because they all give an identical fit to the data. However, biological plausibility would probably lead us to question the validity of the dash-dot trends and, perhaps, the dotted trends as well. Results for males are shown in Fig. 4, and the conclusions are

very similar to those reached for females.

To determine the extent to which the observed trends are real, we must specify how much is likely to be due to artifact, or at least we should identify periods when diagnostic practice may have had a substantial influence on the trends. A crude indication that it has been a factor in the past is indicated by the percentage reported to the tumor registry with only death certificate information, shown in Fig. 5. It is apparent that, in the early years of the Connecticut Tumor Registry, a substantial portion of the cases had only death certificate information, but since 1965, that percentage has been very small. Another indication that the quality of the diagnostic information has improved is suggested by the percentage of the diagnoses that are microscopically confirmed, shown in Fig. 6. Again, the data suggest that the quality of the registry information has been quite good since 1965.

If we assume that the incidence data collected since 1965 have not been influenced by diagnostic artifact, then the period-cohort drift since 1965, *i.e.*, the sum of the slopes, will suggest the real increase for non-Hodgkin's lymphoma in recent years. We estimate the drift by using the period slope for the five intervals since 1965, as well as the slope for the nine most recent cohorts. The estimate of drift is 0.0980 (SE 0.0219) log units/5 years for females, which corresponds to a relative risk of 1.103/5-year period. Similarly, for males the trend is 0.0880 (SE 0.0192) log units/5 years, for a relative risk of 1.092.
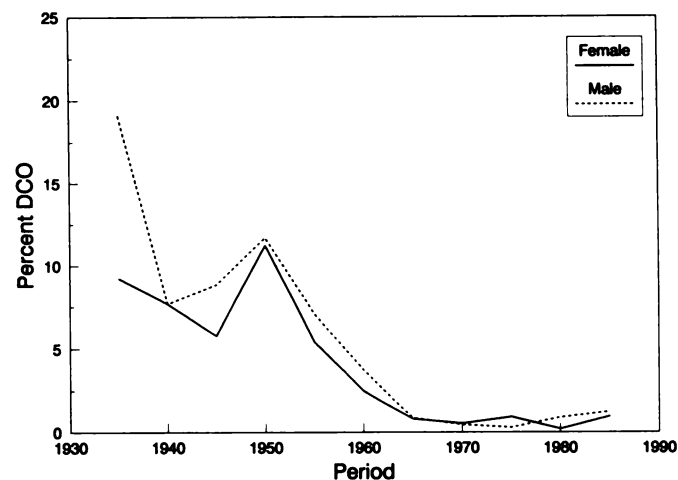

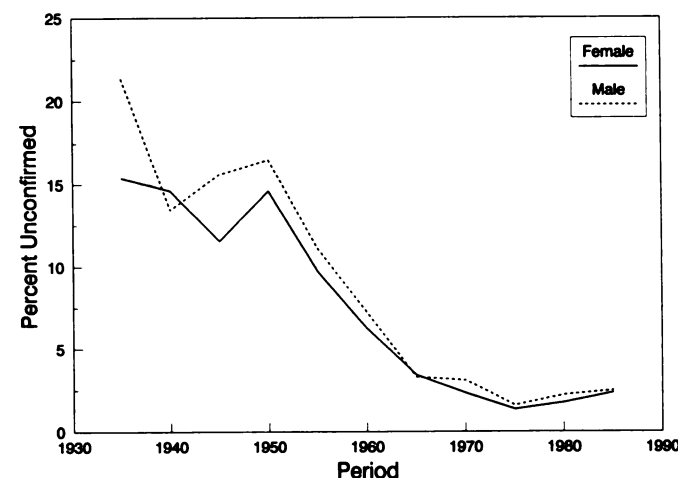Fig. 5. Trends in the percentage of cases reported by death certificate only by sex.

Fig. 6. Trends in the percentage not microscopically confirmed by sex.
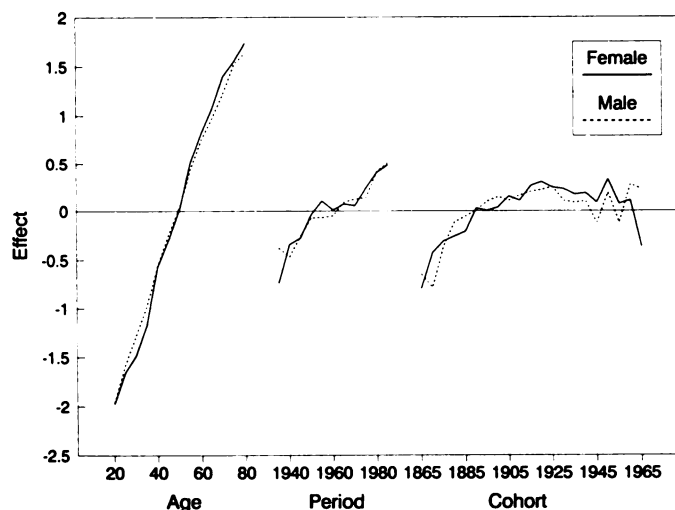
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Fig. 7. Age, period, and cohort effects for females (*solid line*) and males (*dashed line*) constrained so that the sum is 0.

Table 2 *Significance tests for the sex interaction with the curvature effects in the age-period-cohort models for non-Hodgkin's lymphoma incidence rates in Connecticut, 1935–1988*

| Source | d.f. | Likelihood ratio tests | | | |
		Adjusted[a]	P	Unadjusted	P
Age curvature	11	8.70	0.650	8.47	0.671
Period curvature	9	17.84	0.037	16.20	0.063
Cohort curvature	19	18.03	0.520	16.30	0.637

[a] Each interaction with a curvature effect is considered in the presence of the other two.

The trends in the age, period, and cohort effects for males and females are compared in Fig. 7. We obtained a unique trend line for each group by assuming that the slope for the last nine cohorts is zero. While we cannot obtain an estimate of the slope from the data alone, these graphs are useful for comparing the curvature or shape of the trends for females and males. Table 2 presents significance tests that compare the curvatures between the sexes by considering sex-curvature interactions. The adjusted tests include the other interactions, and the unadjusted rates only look at the interactions in the presence of main effects. Only interactions with period appear to be marginally significant. However, the graph shown in Fig. 7 suggests that the magnitude of that difference is rather small, especially for the more recent periods, suggesting that the pattern has been rather similar for males and females.

Discussion

Our analysis of the effects of age, period, and cohort on the trends in non-Hodgkin's lymphoma incidence in Connecticut suggests that both period and cohort effects are involved. Structural limitations of the fundamental time parameters in this model limit the quantities that can be estimated; and we have presented recent trends in terms of the drift or sum of period and cohort slopes. This is a parameter that can be uniquely estimated from the rates (7, 8), and it suggests that there is an increase in the incidence rates that continues through the recent time periods.

In order to determine whether the trends are real, one must keep in mind a variety of artifactual factors that could be related to an increase in reported incidence without changing the true rate. Zheng *et al.* (11) reported that these factors include (*a*)

completeness of registration, (*b*) changes in disease classification, (*c*) advances in diagnostic technology, and (*d*) changes in related diseases such as AIDS.

It is difficult to document the completeness of registration by the Connecticut Tumor Registry, but reporting is thought to be essentially complete since 1965, and since 1971 there has been a legal reporting requirement for all cancer cases occurring in the state (11). Indirect evidence that the tumor registry has been successful in registering cases since 1965 is apparent from the small proportion reported only at death or without microscopic confirmation of the diagnosis. Hence, it is unlikely that incomplete reporting would have very much impact on these estimates of time trends.

Changes in the coding system used to classify the disease resulted in some loss of specificity in cases reported prior to 1961, but the number of cases involved is very low. A more likely source of an artifactual effect might have resulted from advances in diagnostic technology that would have resulted in the detection of more cases over time. Again, it is difficult to quantify the magnitude of this effect. We have estimated a drift of about 9–10%/5-year period, which translates into a 40% increase over 20 years. It seems very unlikely that diagnostic technology would have had this large an impact on the incidence rates for non-Hodgkin's lymphoma.

Finally, the ongoing AIDS epidemic in Connecticut would be expected to have an impact on non-Hodgkin's lymphoma incidence. However, the trend up to this point appears to have started much earlier than the AIDS epidemic. While we would expect to see an effect of AIDS on future trends in non-Hodgkin's lymphoma incidence, it probably has not had much of an effect on the trends reported here.

While data artifact has probably had some impact on the increasing trends in non-Hodgkin's lymphoma incidence, it does not appear to be large enough to account for the magnitude of the effect seen in Connecticut. This leads us to the conclusion that the trends are indeed real. In addition, the significance of an effect due to birth cohort makes it plausible that there have been changes in exposure to unidentified risk factors in the Connecticut population.

References

1. Case, R. A. M. Cohort analysis of mortality rates as an historical or narrative technique. Br. J. Prev. Soc. Med., *10:* 159–171, 1956.
2. Doll, R., and Peto, R. The causes of cancer. J. Natl. Cancer Inst., *66:* 1192–1308, 1981.
3. U.S. Public Health Service. Smoking and Health: A Report of the Surgeon General. Washington, DC: U. S. Department of Health, Education and Welfare, Public Health Service, 1979.
4. Fienberg, S. E., and Mason, W. M. Identification and estimation of age-period-cohort models in the analysis of discrete archival data. *In:* K. F. Schuessler (ed.), Sociological Methodology 1979, pp. 1–67. San Francisco, CA: Jossey-Bass, Inc., 1978.
5. Holford, T. R. Understanding the effects of age, period, and cohort on incidence and mortality rates. Annu. Rev. Public Health, *12:* 425–457, 1991.
6. Holford, T. R. The estimation of age, period and cohort effects for vital rates. Biometrics, *39:* 311–324, 1983.
7. Clayton, D., and Schifflers, E. Models for temporal variation in cancer rates. I. Age-period and age-cohort models. Stat. Med., *6:* 449–467, 1987.
8. Clayton, D., and Schifflers, E. Models for temporal variation in cancer rates. II. Age-period-cohort models. Stat. Med., *6:* 469–481, 1987.
9. Rogers, W. L. Estimable functions of age, period, and cohort effects. Am. Soc. Rev., *47:* 774–796, 1982.
10. GLIM Working Party. The GLIM System, Release 3.77. Oxford, United Kingdom: Numerical Algorithms Group, Ltd., 1987.
11. Zheng, T., Mayne, S. T., Boyle, P., Holford, T. R., and Flannery, J. Epidemiology of Non-Hodgkin's Lymphoma in Connecticut. Cancer (Phila.), in press, 1992.

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